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Title: COVID-19 and cutaneous manifestations: A systematic review

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Abstract

The cutaneous manifestations of COVID-19 patients have been increasingly reported, but not summarized, and the potential mechanisms remain to be investigated. Herein, we performed a comprehensive review of literatures (from inception to May 30, 2020) using PubMed, CNKI, medRxiv, and bioRxiv with the terms "((novel coronavirus) OR (2019 novel coronavirus) OR (2019-nCoV) OR (Coronavirus disease 2019) OR (COVID-19) OR (SARS-CoV-2)) AND ((Dermatology) OR (skin) OR (rash) OR (cutaneous))" and "((ACE2) OR (Angiotensin-converting enzyme)) AND ((skin) OR (epidermis) OR (dermis))". Totally, 44 articles met the inclusion criteria. A total of 507 patients with cutaneous manifestations were summarized, and 96.25% patients were from Europe. The average age of the patients was 49.03 (range: 5-91) with a female ratio of 60.44%. The skin lesions were polymorphic, and erythema, chilblain-like and urticarial lesions were most common, occurring on an average of 9.92 days (range: 1-30) after the onset of systemic symptoms. The receptor of SARS-CoV-2, ACE2, was found to be expressed on skin, mainly on keratinocytes. Our review systematically presented the clinical characteristics of 507 patients and showed that skin might be the potential target of the infection according to ACE2 expression. More work should be done to better understand the underlying pathogenesis.

Introduction

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was firstly reported in Wuhan, China, as an etiological agent causing a new infectious respiratory disease (coronavirus disease 2019, COVID-19) 1. SARS-CoV-2 spread rapidly worldwide through human-to-human transmission and COVID-19 has been declared as a pandemic emergency by World Health Organization (WHO) on March, 2020. By May 30, 2020, 5,701,337 patients were confirmed as COVID-19 cases and 357,688 patients were dead.

The main clinical manifestations of COVID-19 were fever, cough, fatigue, sputum production, dyspnea, and muscle aches2, 3. The diarrhea, olfactory and gustatory impairments caused by COVID-19 were also reported but less common4, 5. An increasing number of literatures on cutaneous manifestations of COVID-19 patients have been recently reported, suggesting that skin lesions could be a potential clinical characteristic of COVID-19. Various viewpoints about the mechanisms inducing the skin rash in COVID-19 patients have been proposed6, 7: 1) Whether the virus could infect through an open wound of skin; 2) Whether skin manifestations were related to immune responses; 3) Whether skin manifestations were caused by a new prescribed medication. However, the researches on the pathogenesis of cutaneous manifestations of COVID-19 have not been performed yet. Given that angiotensin-converting enzyme 2 (ACE2) is a crucial functional receptor of SARS-CoV-28-12. Exploration of the ACE2 expression in skin tissues could facilitate to clarify the mechanisms involved in cutaneous manifestations of COVID-19. Herein, to gain an in-depth understanding of the COVID-19, we summarized the publications related to the cutaneous manifestations of COVID-19 cases and the ACE2 expression in skin tissues.

Methods/Literature Search

A systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched in the Medline database (PubMed), CNKI (https://www.cnki.net/), medRxiv (https://www.medrxiv.org/), and bioRxiv (https://www.biorxiv.org/) with the combined terms "((novel coronavirus) OR (2019 novel coronavirus) OR (2019-nCoV) OR (Coronavirus disease 2019) OR (COVID-19) OR

(SARS-CoV-2)) AND ((Dermatology) OR (skin) OR (rash) OR (cutaneous))" and "((ACE2) OR (Angiotensin-converting enzyme)) AND ((skin) OR (epidermis) OR (dermis))". Searches were limited to the publications before May 30, 2020. Case reports, clinical analysis and fundamental research discussing the cutaneous manifestations and expression of ACE2 in skin were included. Unavailable articles, review articles, expert consensus, medical hypothesis articles, and the articles focusing on the below aspects were excluded: the skin problems of medical staff caused by using protective equipment, the effects of the epidemic on the use of immunosuppressive agents and other drugs in dermatology, the effects of dermatological instruments, and the effects resulted from the treatment of COVID-19 transmission. The cases with clinical diagnosis of the disease (suspected cases) were included in addition to the cases confirmed of COVID-19 by viral nucleic acid detection, viral gene sequencing and serum antibody tests (Supplemental Fig.1).

Results

Study selection and study population

Data from 164 papers were collected. After screening, 120 of them were excluded. We recruited 44 articles, including 38 case reports (Supplemental table 1) and 6 publications of ACE2 expression in skin tissues (Supplemental table 2).

Cutaneous manifestations of COVID-19 patients

Lu *et al.*13 reported a COVID-19 case with urticaria as the first cutaneous manifestation on March 19, 2020. Subsequently, Recalcati *et al.*14 from Italy, Zhang et al.15 from China and Bouaziz et al.16 from France summarized 18, 7 and 14 cases, respectively. In Spain, Fernandez-Nieto et al.[17] and Galván et al.[18] conducted a nationwide case collection survey, and reported 19 and 375 COVID-19 cases with cutaneous manifestations, respectively. However, 17 and 141 of the cases were clinically confirmed rather than diagnosed without etiological evidence, respectively. In addition, 73 sporadic cases have been reported7, 19-49. By May 30, 2020, a total of 507 cases of COVID-19 accompanied by skin manifestations were reported. And 488 out of 507 (96.25%) patients were from Europe.

Basic information

Among the 450 patients reported the basic information, the ratio of male to female was 178/272. The mean age of patients was 49.03 (range: 5-91). According to a previous study of COVID-19 in China, male patients accounted for about 53%, and the average age was 49.5450. Thus, we assumed that the incidence of skin lesions in COVID-19 patients was regardless of ages and genders.

The onset of skin manifestations

Eighty-eight of the 507 patients provided the information on the onset of skin manifestations. Among them, lesions occurred on average 9.92 days (range: 1-30) after the onset of systemic symptoms including fever, cough, dyspnea, diarrhea, and fatigue. In addition, the longest incubation of lesions was 30 days[17], and it was noteworthy that 13 patients (14.77%) had skin lesions as the first symptom17, 25, 26, 29, 31, 45, 47, 49.

Clinical manifestations

All 507 patients had descriptions on their clinical manifestations. We found that the skin symptoms of COVID-19 patients were polymorphic. The most common skin lesion was erythema, which was observed in 224 patients (44.18%) and distributed on patients' trunk, extremities, flexural regions, face, and mucous membranes. Moreover, the erythema lesions were also confined to specific sites, such as the heels14 without other triggers such as exposure. Chilblain-like lesions were described in 100 (19.72%) patients. Urticaria-like lesions were presented in 83 patients (16.37%) and distributed on patients' trunks or dispersed widely on their bodies18. In addition, other manifestations such as vesicular (66, 13.02%), livedo/necrosis (31, 6.11%) and petechiae (8, 1.58%) were described. Significantly, 227 patients (44.77%) complained of significant pruritus. Among the 507 patients, 431 had the information of systematic symptoms. Fever was the most common and presented in 327 patients (75.87%). Other symptoms including cough (299, 69.37%), fatigue or asthenia (252, 58.47%), dyspnea (201, 46.64%), headache (131, 30.39%), gastrointestinal symptoms (116, 26.91%) and anosmia or ageusia (96, 22.27%) were also described.

Skin manifestations and COVID-19 severity

The severity of pneumonia in COVID-19 patients presenting cutaneous manifestations varied.

Zhang *et al.*15 reported 7 COVID-19 patients with critical symptoms. All the patients had extremity ischemia with varied severity, which was manifested as cyanosis, purpura, hemophysallis and dry gangrene. In addition, the skin of two patients become darker than usual after treatment, which might be related to severe symptoms, multiple organ damage and drug treatment51. We speculate that the skin changes in these patients might be caused by multiple organ damages or systemic ischemia, suggesting a severe condition.

For the remaining cases, Only 5 patients had clear information about the severity of COVID-19, including one mild, two ordinary, and two severe cases, according to the diagnostic criteria52. Furthermore, Recalcati *et al*14 argued that the skin manifestations of COVID-19 patients were similar to other skin diseases caused by viral infection, and not related to the severity of pneumonia. According to a study by Galván et al.[18], pseudo-chilblain, vesicular lesions, urticarial lesions, maculopapular lesions and livedoid/necrotic lesions were associated with progressively increasing disease severity.

Lab examinations

Due to the harsh conditions and equipment constraints during the COVID-19 epidemic, only 23 patients performed histopathological examination. All the 23 patients showed inflammatory features without specific pathological changes, such as lymphocyte infiltration20, 24, 40, 41. Amatore *et al.*25 described that no virally induced cytopathic alterations or intranuclear inclusions were present. Sanchez et al.[34], Fernandez-Nieto et al. 39 and Ahouach et al.[35] performed RT-PCR on skin biopsy specimen, andresults were negative for SARS-CoV-2. None of the remaining patients underwent virus detection for skin lesions.

The peripheral blood examination was performed on 39 patients. The most common outcomes were lymphocytopenia (30 patients, 76.92%), C-reaction protein elevation (13 patients, 33.33%), and lactate dehydrogenase (LDH) elevation (18 patients, 46.15%). In the 7 critical patients reported by Zhang *et al.*, D-dimer was significantly increased, and platelet count was normal. Fibrinogen and fibrin degradation product (FDP) were increased in 6 patients, and prothrombin time (PT) was prolonged in 4 patients15. Two patients showed thrombocytopenia, corresponding to a skin lesion that includes petechiae21.

Complications

Ten patients had the complication of hypertension and 6 patients had diabetes. In a study by Galván et al.[18], the number of smokers reached 44, accounting for 11.73% of a total of 375 cases.

Prognosis

For the prognosis of all 507 patients, only 4 cured and 13 dead cases were clearly described. In the seven critical patients, five patients died and the two others were still under treatment after 26 days of follow-up, and the causes of death were circulatory failure resulted from severe hypoxemia and respiratory acidosis15. In addition, a 71-year-old male patient died due to his advanced age and multiple underlying diseases26. In a study by Galván et al.[18], there were 369 survival and 6 dead cases. According to the description of the symptoms, we speculated that most of the patients had a relatively good prognosis and the reported death rate was 2.56% (13/507).

For skin lesions, 39 patients resolved spontaneously or with some basic medication within a week, and other cases did not provide details data. It remains to be discussed whether 7 patients develop skin lesions after taking a drug that targets COVID-19. Although some drugs, such as paracetamol, hydroxychloroquine, and lopinavir/ritonavir, were commonly used with rare adverse reactions, it is still debatable whether the skin lesions were caused by viral infections or adverse drug reactions20, 33, 48, 53.

All the information of the 507 COVID-19 patients were summarized in Table 1.

SARS-CoV-2 entry factors expressed in skin

To our acknowledgement, no studies regarding the mechanisms of devolvement of cutaneous rash in COVID-19 patients have been carried out. Thus, we only summarized the studies linked to the expression of ACE2 in skin tissues. Sungnak *et al.* reported that expression of *ACE2* in skin tissues was not detectable in scRNA-seq datasets11. However, the ARCHS4 database (https://amp.pharm.mssm.edu/archs4/gene/ACE2) showed that *ACE2* was expressed mainly in keratinocytes and basal cells in skin tissues. Furthermore, the expression of *ACE2* has been investigated by bulk samples of human skin54 and in epidermal stem cells55. ACE2

immunoreactivity was detected by immunohistochemistry (IHC) in the cells of the basal layer of the epidermis extending to the basal cell layer of hair follicles, sebaceous gland cells as well as the smooth muscle cells surrounding the sebaceous glands, and the cells of the eccrine glands in normal skin56, 57. Recently, scRNA-seq was applied to analyze the *ACE2* mRNA expression in different cell types in skin tissues58. Higher *ACE2* expression was identified in keratinocytes mainly in differentiating keratinocytes and basal cells compared to the other cells of skin tissues. The results were further confirmed by IHC, which showed the ACE2-positive keratinocytes in the stratum basal, the stratum spinosum, and the stratum granulosum of epiderma. In addition, Li *et al.* found that CD8+ T cell enrichment had significant positive correlations with the *ACE2* expression in the skin59.

Discussion

Infection with SARS-CoV-2 causes a broad spectrum of clinical syndromes, ranging from mild pneumonia to acute respiratory distress syndrome. Although cutaneous manifestations are rare, the number of COVID-19 patients with skin involvement has been reported to be increased. However, up to date, no *in vitro* or *in vivo* experiments have been performed to confirm whether SARS-Cov-2 could spread through skin. In this review, we found that ACE2 was expressed in the skin, especially in keratinocytes. This provides an evidence for percutaneous infection or the entry of virus into patients through skin tissue. Furthermore, SARS-CoV-2 RNA was detected in blood samples from 22% patients60. Thus, it is possible that the ACE2 expression in skin cells could be induced by viral infection via hematogenous dissemination, especially for the patients who were in a state of viraemia. More biopsy specimens should be collected to detect whether the presence of virus in skin lesions to confirm it.

According to our review, erythematous rash is the most common feature among 507 patients. However, the mechanisms of erythema development in the COVID-19 patients remain unclear. It has been found that herpes simplex virus (HSV) could cause a subset of erythema multiforme (EM) lesions (herpes-associated EM (HAEM))61. After infection by HSV, the DNA of HSV would be fragmented and the DNA fragments could be transported to distant skin sites by

peripheral blood mononuclear cells (PBMC). The HSV-specific CD4+ Th1 cells could be recruited by the viral antigen to skin and initiate an inflammatory cascade, which induces the development of HAEM. For SARS-CoV-2 infection, although no studies have reported virus in skin lesions, hyperactivated CD4+ and CD8+ T cells were found in peripheral blood from patients by flow cytometry. Moreover, the concentration of CCR4- and CCR6-positive Th17 in CD4 T cells was increased. CCR4 has been implicated in the migration of T cells into skin, and its ligand, CCL17, is expressed on cutaneous endothelial cells62. Thus, the virus-specific T cells in circulation could migrate into skin tissues. In addition, lymphocyte infiltration has also been observed in the skin lesions of COVID-19 patients. These findings suggested that the skin rash might be caused by the virus-specific T cells.

Urticaria is another common feature among those COVID-19 patients who presented rashes. Previous studies hypothesized that viral IgM and IgG could cross react with mast cell IgE, and cause the mast cell degranulation subsequently63. SARS-CoV-2- specific IgM and IgG can be detected in patients64. Thus, the cross reaction between SARS-CoV-2 antibodies with mast cell IgE might result in degranulation of mast cell and wheal growth.

Chilblain-like lesions, ischemic lesions and ecchymotic acral lesions were also observed in COVID-19 patients. It has been reported that blood coagulation is altered in COVID-19 patients and the acro-ischemia might be associated with the hypercoagulation status in severe COVID-19 patients15. Recently, these types of skin lesions were also found in asymptomatic or mildly symptomatic patients, probably caused by a coagulation disorder or a hypersensitivity reaction17, 65. Unfortunately, the mechanisms of cutaneous manifestations are only hypothetical at present.

Interestingly, it is likely that the incidence of skin rashes among COVID-19 patients varied in different countries. Only eight cases were reported in China whereas 488 cases were from Europe. A study in China reported that only two of 1,099 patients showed skin lesions66, whereas Recalcati *et al.*14, an Italian dermatologist team, described that skin changes occurred in 18 of the 88 confirmed COVID-19 patients, and Hedou *et al.*67 reported that the incidence of cutaneous manifestations associated with COVID-19 infections in France was 4.9% based on a prospective study of 103 cases. It is unclear that whether the difference was caused by missed diagnoses and

unreported cases, or regional differences.

It is noteworthy that skin rashes are also observed in general population. For example, in a population-based study, up to 1% of the general population in the USA and Europe suffered from chronic urticarial at some point in their lifetime68. The ratio was significantly higher in Asia, which was about 9-20%69. Urticaria-like lesions were presented in 16.37% COVID-19 patients with skin manifestation in our study. Therefore, we could not rule out that the cutaneous lesions of COVID-19 patients were merely an incidental phenomenon based on the population incidence.

Conclusions

In conclusion, our review summarized the clinical characteristics of skin lesions in COVID-19 patients and the possible mechanisms by reviewing the ACE2 expression in skin tissues. However, we should acknowledge that lots of questions regarding COVID-19 remain unexplored. More clinical data should be collected, and more researches should be carried out for a better understanding of the cutaneous manifestations caused by COVID-19.

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Table 1. Summary of the demographics and clinical characteristics

Basic information	
Total number of cases	507
Female sex - no. (%)	272/450 (60.44%)
Mean age (range) - years	49.03 (5-91)
Country (n=507) - no. (%)	
Spain	434 (85.60%)
Italy	33 (6.51%)
France	19 (3.75%)
China	8 (1.58%)
American	5 (0.99%)
Canada	3 (0.59%)
Belgium	2 (0.39%)
Thailand	1 (0.20%)
Indonesia	1 (0.20%)
Japan	1 (0.20%)
Mean time of appearance of skin lesions after onset of COVID-19 (range) - days	9.92 (1-30)
Cutaneous manifestations (n=507) - no. (%)	
Erythema	224 (44.18%)
Chilblain-like lesions	100 (19.72%)
Urticaria-like lesions	83 (16.37%)
Vesicular	66 (13.02%)
Livedo/necrosis	31 (6.11%)
Petechiae	8 (1.58%)
Accompanied by pruritus	227 (44.77%)
Mean duration of skin lesions - days	9.10
Information of COVID-19 (n=507) - no. (%)	
Confirmed cases	343 (67.65%)

Suspected cases	164 (32.35%)
Systemic symptom (n=431) - no. (%)	
Fever	327 (75.87%)
Cough	299 (69.37%)
dyspnea	201 (46.64%)
Fatigue or asthenia	252 (58.47%)
Anosmia or ageusia	96 (22.27%)
Headache	131 (30.39%)
Gastrointestinal symptom	116 (26.91%)
Complications and Medical History - no. (%)	
Smoking	44/375 (11.73%)
Hypertension	10/18 (55.56%)
Diabetes	6/18 (33.33%)
Lab examinations - no. (%)	
Histopathology	23/507 (4.54%)
Lymphocytopenia	30/39 (76.92%)
Elevated CRP	13/39 (33.33%)
Elevated LDH	18/39 (46.15%)
Case fatality - no. (%)	13/507 (2.56%)